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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,103	04/12/2001	Aki Kitagawa	12372-002001	5320

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/02/2004

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,103	KITAGAWA ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,21 and 23-46* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 26-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-18,20,21 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II (claims 12-25) in Paper No. 8 dated June 26, 2002 is acknowledged.

2. Claims 1-11 and 26-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8 dated June 26, 2002.

Priority

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Applicant's Response dated July 11, 2003

4. In the Response filed July 11, 2003, claim 12 was amended; claims 19 and 22 were canceled. Applicant presented arguments directed to the rejection of claims 12-18, 20-21, and 23-25 under 35 U.S.C. 103(a). Claims 1-18, 20-21, and 23-46 are pending. Claims 1-11 and 26-46 are drawn to a nonelected invention. An action on the merits of claims 12-18, 20-21, and 23-25 is contained herein below.

5. Applicant's arguments with respect to claims 12-18, 20-21, and 23-25 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

6. Claims 12-18, 20-21, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. EP 0 913 149 A1 (Suzuki) in view of the combination of Igari et al US 5,344,644 (Igari) and Hasegawa et al. US 4,675,184 (Hasegawa).

Claims 12-18, 20-21, and 23-25 are drawn to a method of producing a sustained release protein drug composition comprising providing a precipitating solution containing a mucopolysaccharide, a carrier protein, and a protein drug; lowering the pH of the solution to form an insoluble product; and collecting from the solution the insoluble product.

Suzuki teaches drug compositions with controlled drug release rates (page 2, lines 35-49). The compositions comprise a matrix formed from (**a**) and (**b**), wherein (**a**) is a biodegradable, biocompatible high-molecular substance and/or polyvalent metal ions or polyvalent metal ion source and (**b**) is hyaluronic acid or a salt thereof; and a drug (**c**) (page 2, lines 35-49). Examples of biodegradable, biocompatible high-molecular substances include gelatin, sodium casein, albumin, and lysozyme chloride (page 3, lines 11-17). Preferred polyvalent ions include Ca^{2+}, Al^{3+}, and Fe^{3+} (page 3, lines 16-19). A wide variety of drugs may be used including but not limited to anti-inflammatory drugs, hypnotic sedatives, stimulants, ophthalmic drugs, cardiacs,

diuretics, antibiotics, antitumor agents, chemotherapeutic agents, and vitamins (page 3, lines 33-48). The content of ingredient (**a**) in the composition may range from 5 to 95 wt.% (page 3, lines 23-24). The content of ingredient (**b**) may range from 50 to 80 wt.% (page 3, lines 45-48). The composition may further comprise excipients, stabilizers, preservatives, surfactants, buffers and the like (page 4, lines 10-11).

Suzuki teaches a submerged hardening method for producing the composition (page 4, lines 37-49). According to the method, a solution of the hyaluronic acid or salt thereof (**b**) is added to a hydrophobic solvent and emulsified. The formed emulsion is then added under stirring to a solution of a biodegradable, biocompatible high-molecular substance and/or polyvalent metal ions or polyvalent metal ion source (**a**). After the resulting mixture is stirred, microcapsules are allowed to form. The microcapsules are collected by filtration, washed and then dried, whereby microcapsules are obtained as the drug composition. The drug (**c**) may generally be added beforehand in the solution of (**a**) and/or the solution of (**b**) unless addition of (**c**) in a different manner is required for its physical and/or chemical properties. Suzuki further teaches the addition of albumin (**a**) in an acidic solution (page 7, Examples 33-34).

Suzuki differs from the instantly claimed invention in that Suzuki does not limit the method to protein drugs. Suzuki does not explicitly disclose lowering the pH for the purpose of precipitating the protein drug composition; however, one of ordinary skill in the art would recognize that the addition of an acidic solution would indeed lower the pH of the solution. Suzuki does disclose the use of γ-globulin as a carrier protein. Suzuki

does not disclose lyophilizing a preparatory solution with a pH of 6 to 8 to obtain the product.

Igari teaches a method for preparing sustained-release compositions. The compositions comprise a pharmaceutically active agent (column 3, lines 52-59). Pharmaceutically active agents which may be used include interferons (e.g. alpha, beta, gamma), interleukins (e.g. IL-2 to IL-11), erythropoietin, granulocyte colony stimulating factors, granulocyte-macrophage colony stimulating factors, thrombopoietin, insulin, growth hormones, and parathyroid hormone related peptide (columns 3-4). The composition may further comprise a mucopolysaccharide such as chondroitin sulfate, heparin, and keratan sulfate (column 5, lines 16-65). The composition may further comprise water-soluble proteins such as serum albumin, globulin, collagen, or gelatin (column 6, lines 7-15). The weight ratio between the water-soluble protein and the mucopolysaccharide is 0.00001:1 to 100:1 (column 6, lines 16-23). Igari teaches that lowering the pH of the composition below 4 will cause the formation of a precipitate (column 6, lines 43-52). The pH of a solution prepared from the water-soluble composition should be such that said pH will not exert any adverse influence upon the activity of the pharmacologically active peptide. Igari also teaches that the composition may be in a form dissolved in water or in a lyophilized form (column 7, lines 31-33). The compositions may be made by admixing the ingredients using conventional methods (column 7, lines 56-68).

Hasegawa teaches a pharmaceutical composition containing interferon in a stable state which comprises 60% by weight of a tri or higher polyhydric sugar alcohol

and an organic acid buffer as stabilizers, and a conventional pharmaceutically carrier or diluent (Abstract). The pH of the composition is about 3 to 6. Optionally, the composition can further contain as a stabilizer an anionic surfactant and/or albumin. The composition can be prepared in various forms suitable for application in the oral cavity, topical application to the skin, rectal, vaginal and urethral administration, application to the eye, the nose and the throat, etc. and interferon in the composition can maintain its activity for a long period of time (column 1, lines 43-59).

It would have been obvious to one of ordinary skill in the art at the time of the invention to lower the pH of the preparatory solution as described by Suzuki below 4 (i.e. about 3) since Igari teaches that lowering the pH causes precipitation. Suzuki does not explicitly teach lowering the pH for the purpose of precipitating drug composition out of solution; however, one of ordinary skill in the art would recognize that the addition of an acidic solution would indeed lower the pH of the solution. The reference does not have to explicitly state what the reference specifically teaches. All of the compositions described by Suzuki are ultimately obtained by precipitation. It would have been obvious to one of ordinary skill in the art at the time of the invention to lower the pH (i.e. add acid) of the preparatory solution in order to precipitate the drug composition since Igari teaches that the lowering the pH of sustained-release compositions below 4 will cause the formation of a precipitate. One of ordinary skill in the art would have a reasonable expectation of success in precipitating a protein drug (interferon) at a pH 3-6 without lose of activity since Hasegawa teaches use of organic acid buffers at pH 3-6 to stabilize interferon compositions. It would have also been obvious to one of ordinary

skill in the art to use γ-globulin as a carrier protein since Igari teaches the use globulins (also teaches serum albumin, collagen, and gelatin) as carrier proteins for forming sustained-release compositions. Igari also teaches that the composition may be in a lyophilized form. Being that Igari and Suzuki teach very similar compositions it would have been obvious to the skilled artisan that composition as disclosed by Suzuki may also be in a lyophilized form. Modifications of Suzuki to obtain the instantly claimed invention are seen to be a choice of experimental design and would have been well within the purview of the skilled artisan in the field. Optimization of reaction conditions, i.e. pH, manner of adding reagents, ratio of reactants, do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such condition is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Conclusion

7. Claims 1-18, 20-21, and 23-46 are pending. Claims 1-11 and 26-46 are withdrawn from consideration as being drawn to a nonelected invention. Claims 12-18, 20-21, and 23-25 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

ptl
February 25, 2004

James O. Wilson
Supervisory Patent Examiner
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